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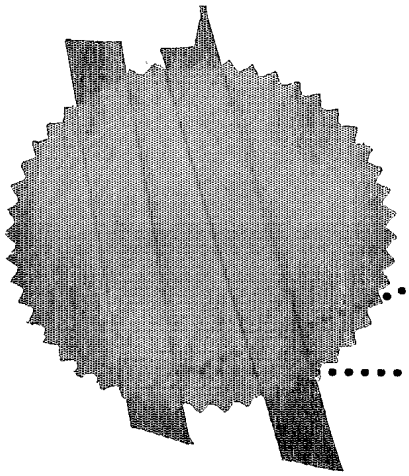
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 23/02/2004 in respect of Patent Application No.219/MUM/2004 of **M/S. CADILA HEALTHCARE LIMITED**, a company incorporated under the Companies Act, 1956 of Zydus Tower, Satellite Cross Road, Ahmedabad – 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act,1970.



Dated this 26th day of May 2005.

(RAKESH KUMAR)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

1. We, **M/s Cadila Healthcare Limited**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

2. Hereby declare-

   a) That we are in possession of an invention titled
   "A novel and economic method of preparation of α blocker agent i.e. Carvedilol"

   b) That the provisional specification relating to this invention is filed with this application.

   c) That there is no lawful ground of objection to grant of a patent to us.

ORIGINAL

3. Further declare that the true and first inventors for the said invention are:

1)	***SHAH, Dhiraj, R.***	*(Indian Citizen)*
2)	***NAIK,Ashish P.***	*(Indian Citizen)*
3)	***PUROHIT, Parva Y.***	*(Indian Citizen)*
4)	***SHARMA, Rajivkumar***	*(Indian Citizen)*
5)	***AGARWAL, Virendra K.***	*(Indian Citizen*

4. We, claim the priority from the application filed in convention countries, particulars of which are as follows: **NIL**

5. That we are the assignee or legal representatives of the true and first inventors.

6. That our address for service in India is as follows:

   M/s Subramaniam, Natraj & Associates
   Attorneys-At-Law
   E-556, Greater Kailash-II
   New Delhi - 110 048, India.

   Phone: +91 11 29215603, 29226012, 29216025
   Facsimile: +91 11 29226005
   Email: sna@vsnl.com

219/MUM/2004
Dt: 23/2/04

Received Rs. 3550/- in Cash
Cheque/M.O./P.O. on 23/2/04
Vide Entry No. 8912 in the Register of Valuables, Bombay

7. Following declaration was given by the inventors:

SHAH, Dhiraj,R an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

NAIK, Ashish,P, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

219 | मुंबई | MUM | 2004

23 FEB 2004

PUROHIT, Parva Y, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

SHARMA, Rajivkumar, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

AGARWAL, Virendra Kumar, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

We, the true and first inventors for this application, declare that the applicants herein are our assignee:

SHAH, Dhiraj,R

NAIK, Ashish, P

PUROHIT, Parva Y

SHARMA, Rajivkumar

AGARWAL, Virendra Kumar

8. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

9. Following are the attachment with the application:
   a) Provisional specification (3 copies)
   b) Application form 1 in triplicate.
   c) Statement and undertaking in FORM-3.
   d) Abstract.

Fee Rs._____ /- in Cash/ Cheque/ bank draft bearing No. _____ date _____ on _____ Bank.

We request that a patent may be granted to us for the said invention.

To,
The Controller of Patents
The Patent Office
At Mumbai

Date: 16.2.2009

Signature: _____
Name: Arun Parikh
Designation: Sr. Vice President
For **Cadila Healthcare Limited**

FORM 2

The PATENT ACT, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

A NOVEL AND ECONOMICALLY VIABLE METHOD FOR THE PREPARATION OF CARVEDILOL

ORIGINAL

CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

The following specification describes the nature of the invention:

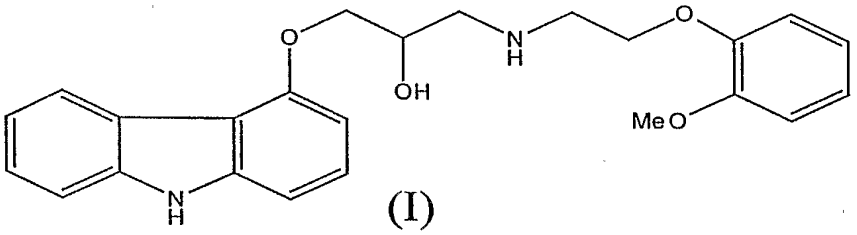
Field of invention

The present invention relates to an economically viable process for manufacture of racemic carvedilol. In particular, the present inventionrelates to a process for manufacture of racemic carvedilol salt of high HPLC purity (> 99.5%) having individual impurity less than 0.1%.

As per this process, carvedilol is isolated by salt formation with suitable organic acids. The salt is purified and treated with a base to produce the aforesaid product of high HPLC purity.

Background of the invention:

Carvedilol, chemically known as (±) 1-(4-carbazolyloxy)-3-[2-(2-methoxyphenoxy) ethyl]amino-2-propanol has the following structural formula (I):



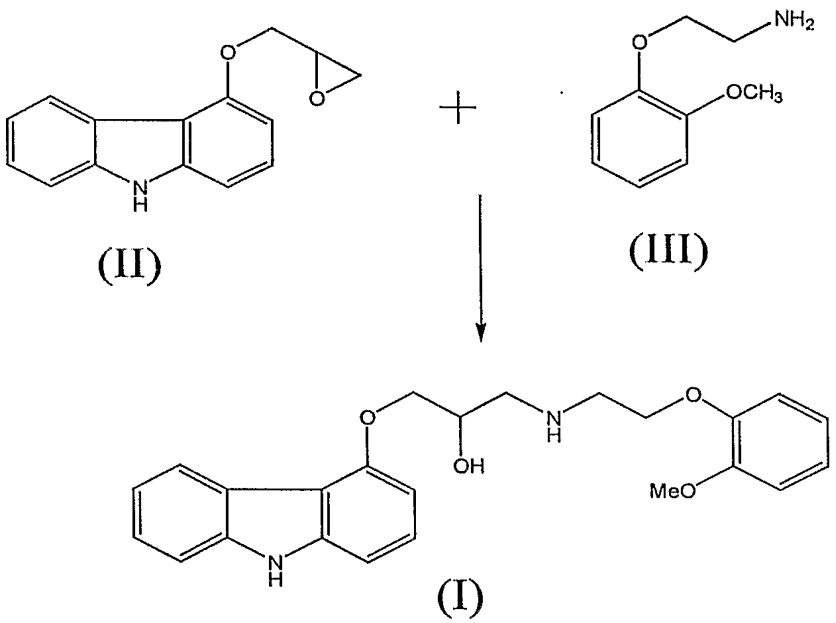
(I)

It is a nonselective β-adrenergic blocking agent with α_1 blocking activity. Carvedilol has an asymmetric carbon and exists either as individual stereoisomers or in racemic form. The nonselective β-adrenergic activity of carvedilol is present in the S (-) enantiomer and α_1 blocking activity is present in both the R(+) and S(-) enantiomers at equal potency. It is marketed in racemic form.

Various procesees are known in the prior art for the preparation of carvedilol. EP 129099 describes the preparation of both the racemate and stereoisomers.

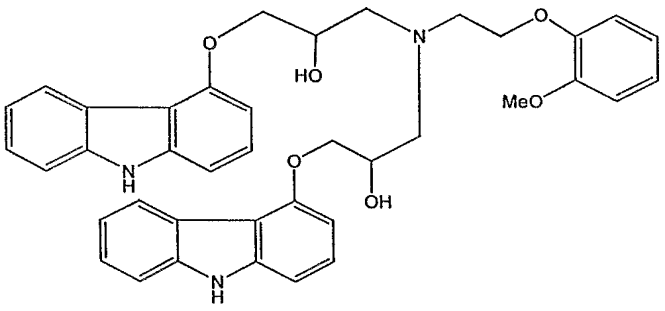
US 4503067, US 4824963,EP 129099, EP 918055, EP 1142873, WO 02/00216 are incorporated herein by reference & disclose various processes for preparing carvedilol.

US 4503067 discloses a process for preparation of carvedilol by the following reaction scheme – I.



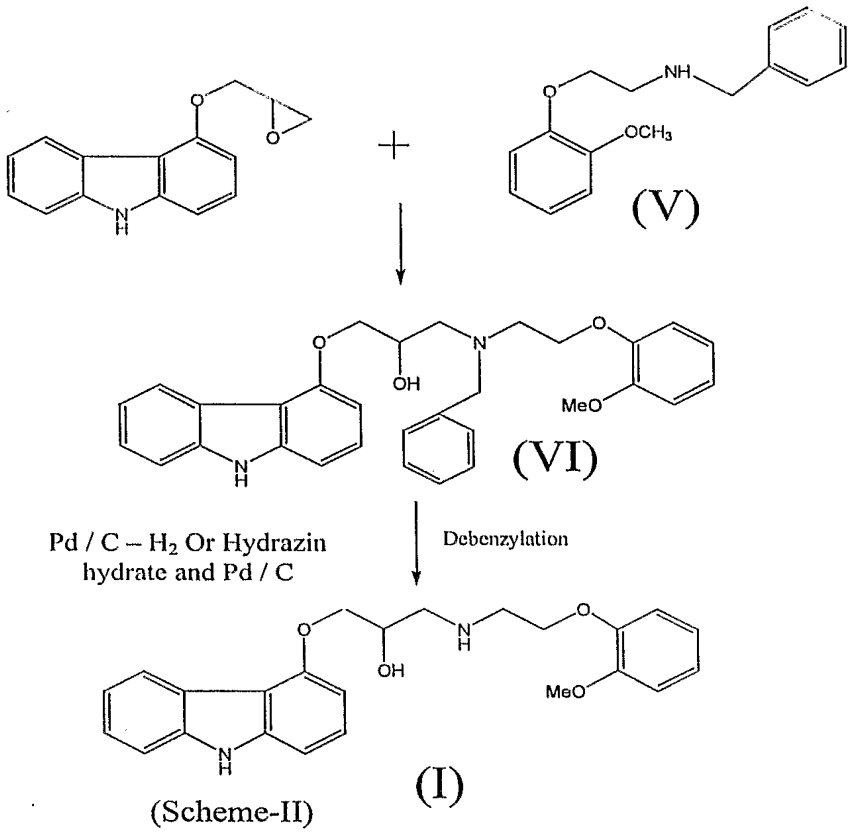
(Scheme-I)

4-(oxiran-2-ylmethoxy)-9H-carbazole (II) is reacted with 2-(2-methoxy phenoxy)ethylamine (III) in a molar ratio of 1:1.1 and the reaction is carried out at 50°C temperature for 25 hours. The process gives low yield of 39.42%. A considerable amount of by-product (formula IV) is formed, resulting in a low yield of desired product and making the purification difficult.



(IV)

EP 918055 A1, EP 1142873 A2 discloses the preparation of carvedilol as mentioned in scheme – II



(Scheme-II)

The process involves the catalytic N-debenzylation at final stage. It is known that N-debenzylation reaction never goes for 100% completion, leading to traces of N-benzyl Carvedilol (VI) as major impurity in final product. European Pharmacopoeia has covered the limit of this impurity (VI) not more than 0.02% due to its toxic nature and practically it is difficult to achieve this level by the process based on above scheme II.

Recently US 2002/0143045A1 discloses the preparation of carvedilol by reaction of 4-(oxiran-2-ylmethoxy)-9H carbazole (II) with 2-(2-methoxyphenoxy)ethylamine (III) in 1 : 1.5 to 1: 100 molar ratio without solvent in neat condition at 100°C to minimize the formation of compound (IV) as by-product. This specification does not disclose the yield and the purity of the carvedilol obtained. At higher temperature and in the absence of solvent there is a possibility that some degradation may occur, resulting in a low yield. The use of large amount of 2-(2-methoxyphenoxy) ethylamine (III) makes the process uneconomical.

Objectives of the present invention:

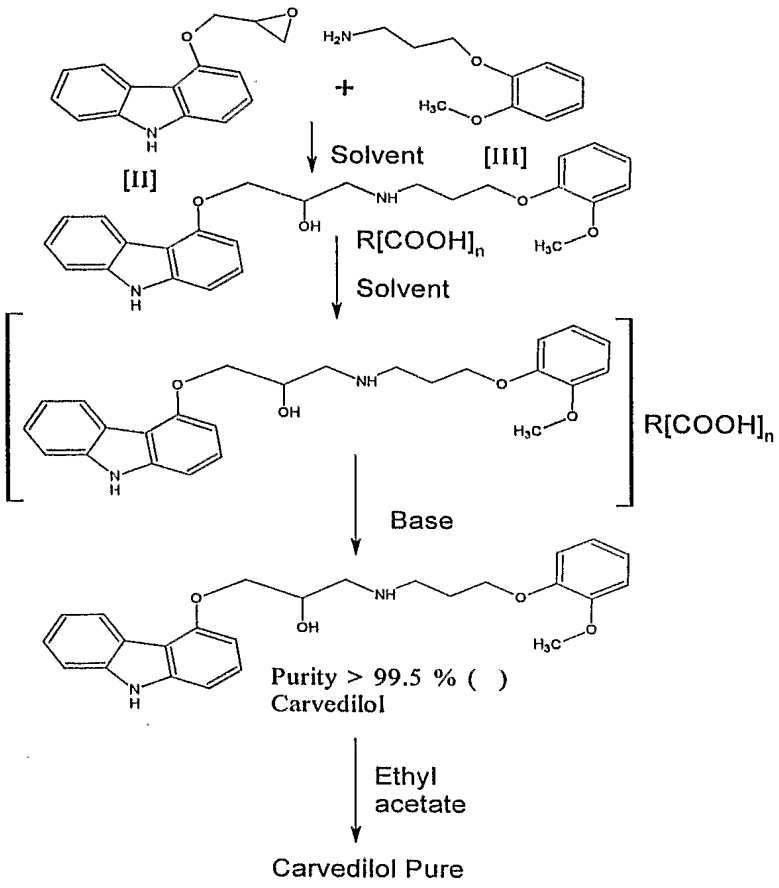
It is evident from above that though prior art looks conceptually very good but practically it is very difficult to implement at large scale production. According to the US 4503067, the reaction time itself is 25 hrs with lesser yields. While in WO 0200216 the product is crystallized out in 40 hours at 4°C and as per EP 0918055, the final stage involves catalytic hydrogenation for debenzylation. Thus these processes are not feasible on production scale.

Main objective of the present invention is to prepare pure carvedilol by an economically viable process. More specifically the objective of the present invention is to disclose a process for manufacture of carvedilol having purity (> 99.5%) with individual impurities less than 0.1% by removing drawbacks of the prior arts.

Detailed description:

Accordingly the present invention provides a simplified process for the preparation of pure carvedilol which involves condensation of Compound (II) and (III) in described molar ratio in the presence of preferred solvent, preparation of the salt of carvedilol with suitable organic acid in a preferred solvent, isolation and purification of the salt to get pure carvedilol from the salt by treatment with a base. Carvedilol thus obtained is purified to get required quality & polymorphic form of the product.

The embodiment is disclosed in the scheme-III



(Scheme-III)

4-(oxiran-2-ylmethoxy)-9H-carbazole (II) is reacted with 2-(2-methoxy phenoxy)ethylamine (III) in a molar ratio of 1:1.15 to 1:1.45, preferably in a molar ratio of 1:1.4.

This reaction is carried out at 30 – 90°C, preferably at 50 – 80°C, most preferably at 70-80°C in a suitable solvent such as primary, secondary or tertiary lower alcohol containing 1-6 carbon atoms, esters i.e. CH_3COOR, where R= straight or branched chain alkyl group containing 1-4 carbon atoms, nitrile R-CN where R is straight or branched chain alkyl group containing 1-4 carbon atoms.

The preferred solvent is Methanol, Ethanol, 2-propanol, isobutanol, ter.butanol, acetonitrile, ethylacetate. Preferred solvent is 2-propanol. The reaction is carried out for 10 min to 20 hrs, preferably for 40 to 90 minutes, preferably for 60 minutes.

After completion of reaction, the reaction mass is then added to a solution of carboxylic acid having general formula R'(COOH)n whereas n=1 and R' = (un) substituted aryl group i.e. Benzoic acid & Salicylic acid & n=2 and R'= (un) substituted alkyl group i.e. Oxalic acid & tartaric acid, in a suitable solvent as described above. Preferred carboxylic acid is Salicylic acid.

During the addition of reaction mixture into the solution of carboxylic acid, the temperature is maintained at 20°C to 90°C, preferably at 75-85°C. The precipitated salt of carvedilol is isolated by known art i.e. filtration or centrifugation. This salt contains about 1.5-2.5% of compound IV as a major impurity.

The salt is purified by crystallization from an organic solvent. Organic solvent is selected from primary, secondary or tertiary aliphatic alcohol containing 1-4 carbon atoms, esters CH_3COOR where R is a mentioned above, preferably ethyl acetate. This crystallization is reduced the amount of impurity to about 1-1.5%.

The salt is then treated with suitable organic or inorganic base in water-solvent system to get carvedilol. Inorganic base is selected from alkali metal carbonate, bicarbonate or hydroxides. Organic base is selected from a straight, branched or cyclic primary, secondary or tertiary aliphatic amine containing 1 to 6 carbon atoms. Preferred inorganic base is Sodium Hydroxide while organic base is triethylamine.

Organic solvent is selected from primary, secondary or tertiary aliphatic alcohol containing 1-4 carbon atoms, esters CH_3COOR where R is a mentioned above, preferably ethyl acetate and 2-propanol.

Carvedilol is then isolated by known processes such as filtration or centrifugation and then finally purified by crystallization from an organic solvent. Organic solvent includes primary, secondary or tertiary aliphatic alcohol having containing 1-4 carbon atoms, esters such as CH_3COOR where R containing straight or branched chain alkyl group having containing 1-4 carbon atoms. The product is again recrystallized from the same solvent. The most preferred solvent is Ethylacetate.

Advantages of the present invention:

1. Quantity of 2-(2-methoxyphenoxy)ethylamine used is reduced.

2. The reaction is conducted in a solvent at a reflux temperature. This reduces reaction time and avoids high temperature.
3. The product is isolated as a salt and the salt is purified. This gives a final product of better quality, while all the major impurities go into the mother liquor.
4. Carvedilol obtained by the disclosed embodiment complies with European Pharmacopeia pharmaceutical specifications.
5. Organic acid is recovered and recycled.
6. Due to high yield and purity disclosed embodiment is commercially viable.

The present invention will be more fully understood from the examples given below, but the examples do not necessarily exemplify the full scope of the invention.

Example: 1

Preparation of carvedilol salicylate

A mixture of 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (25g, 104.60 mmole) and 62.5ml 2-propanol was heated to 70–80°C. To this, 2-(2-methoxyphenoxy)ethylamine (III) (20.96g, 125.52 mmole) was added in one lot. The temperature of the reaction mass was raised to 80 – 85°C and refluxed for 1 hour. The reaction mixture was added into the pre-heated (80 – 85°C) solution of salicylic acid (18.77g, 135.98 mmoles) in 187.5 ml 2-propanol. This reaction mass was further refluxed for 2 hr, cooled to 50 – 55°C and stirred for 1 hr at this temperature. The solid was filtered and washed with hot 2-propanol (50 – 55°C) (3x 33 ml). The wet product was dried at 60-65°C for 6 hrs or till constant weight, & gave 32.5 g of carvedilol salicylate (Yield=57%).

This contains about 2-2.5% of compound (IV) as an impurity.

HPLC Purity = 92.5-95%

M.P. = 164 – 166°C

Example: 2

A mixture of 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) (25g, 104.60 mmole) and 62.5ml 2-propanol was heated to 70–80°C. To this, 2-(2-methoxyphenoxy)ethylamine (III) (25.33g, 151.67 mmole) was added in one lot. The temperature of the reaction mass was raised to 80 – 85°C and refluxed for 1 hr. The reaction mixture was added into the pre-heated (80 – 85°C) solution of salicylic acid (18.77g, 135.98 mmoles) in 187.5 ml 2-propanol. This reaction mass was further refluxed for 2 hours, cooled to 50 – 55°C and stirred for 1 hour at this temperature.

The solid was filtered and washed with hot 2-propanol (50 – 55°C) (3x 33 ml). The wet product was dried at 60-65°C for 6 hrs or till constant weight, gave 39.75 g of Carvedilol Salicylate (Yield=70%).

This contains about 2-2.5% of compound (IV) as an impurity.

HPLC Purity = 92.5-95%

M.P. = 164 – 166°C

Example: 3

Process of purification for Carvedilol Salicylate:

A mixture of carvedilol salicylate (39g, 39.81 mmole) and ethyl acetate (312 ml) was stirred at 70 – 75°C for 30 minutes, then cooled to 50– 55°C and stirred at same temperature for 1 hour, filtered at same temperature and washed with hot (50-55°C) ethyl acetate, dried at 60-65°C for 6 hrs or till constant weight gave 37g of pure carvedilol salicylate (Recovery=94.87%).

This contains about 1.0-2.0 % of compound (IV) as an impurity.

HPLC purity = 94-97 %

M.P. = 165 – 167 °C

Example: 4

Preparation of Carvedilol Benzoate:

A mixture of 25 gm (104.60 m mole) 4-(oxiran-2-yl methoxy)-9H-carbazole (II) and 62.5 ml 2-propanol was heated to 70 – 80°C .To which 25.33 g (151.67 mmole) of 2-(2-methoxyphenoxy) ethylamine (III) was added in one lot. The temperature of mass was raised to reflux (80 – 85°C) & then maintained this reaction temperature for 1 hr. After that, this reaction mass was added to the pre-heated (80 – 85°C) solution of benzoic acid (18.5g) in 2-propanol (287.5 ml) and continued the reflux for next 2 hr. Now cooled to 50 – 55°C and maintained the same temperature for 1 hr. The product was filtered at same temperature (50 – 55°C) and washed the cake with 3 x 33.5 ml of hot 2-propanol (50 – 55°C). Dry the product at 60 – 65°C for 6 – 8 hr or till constant weight gave 36.5g of Carvedilol benzoate (Yield = 66%).

Example: 5

Preparation of Carvedilol Tartrate:

A mixture of 25g (104.60 mmole) of 4-(oxiran-2-yl methoxy)-9H-carbazole (II) 25.33 g (151.67 mmole) and 62.5 ml 2-Propanol was heated to 70-80°C. To which of 2-(2-methoxyphenoxy) ethylamine (III) was added in one lot. The temperature of reaction mass was raised to reflux (80-85°C) and maintained this temperature for 2 hr. After that, this reaction mass was added to the pre-heated (80-85 °C) solution of L(+) tartaric acid (24.32 g) (0.1621 m mole) in 2-propanol (287.5 ml) and continued the reflux for next 1 hr, cooled to 50-55°C and maintained for 1 hr. The product was filtered at the same temperature (50-55°C) and washed the product with 3 x 33.5 ml of hot (50-55°C) 2-Propanol. Dry the product at 60-65°C for 6-8 hrs or till constant weight gave 33.0 g. of Carvedilol tartrate. (Yield = 56.89%).

Example: 6

Preparation of Carvedilol Oxalate:

A mixture of 25 g (104.60 m mole) of 4-(oxiran-2-yl methoxy)-9H-carbazole (II) and 62.5 ml 2-Propanol was heated to 70-80°C. To which, 25.33 g (151.67 m mole) of 2-(2-methoxyphenoxy) ethylamine (III) was added in one lot. The temperature of reaction mass was raised to reflux (80-85°C) and maintained this temperature for 1 hr. After that, this reaction mass was added to the pre-heated (80-85°C) solution of oxalic acid (14.6 g) (162.13 m mole) in 2-Propanol (287.5 ml) and continued the reflux for next 2 hr, cooled to 50-55°C and maintained for 1 hr. The product was filtered at the same temperature and washed with 3 x 33.5 ml of hot (50-55°C) 2-Propanol. Dry the product at 60-65°C for 6-8 hrs or till constant weight gave 42 g. of Carvedilol Oxalate

(Yield = 80.95%)

Example: 7 (A)

Preparation of Carvedilol fom Carvedilol Salicylate:

A mixture of Carvedilol salicylate (36g, 66.18 mmole) and 2-propanol (108 ml) was heated to 50 – 55°C. To this, a solution of sodium hydroxide (4.5g) in water (36 ml) was added slowly in about 30 min. The solution was then stirred at 65 – 70°C for 15 min. and filtered,

washed with hot (55 – 60°C) 2-propanol (2x 18 ml). The filtrate was cooled to 30 – 40°C, 18 ml of water was added and stirred at 25 – 35°C for 3 hr. The precipitated product was filtered and washed with 2x30 ml of water, dried at 50 – 55°C till constant weight gave 24.5g of Carvedilol (Yield=91.21 %)

HPLC purity 98.5-99.5%

Impurity (IV) 0.5% to 1.0%

Example: 7 (B)

Preparation of Carvedilol from Carvedilol Salicylate:

A mixture of Carvedilol salicylate (25g, 45.95 mmole) and Ethyl acetate (250ml) was cooled to 10-15°C. To this solution Triethylamine (10.16g, 100.63 m mole) was added within 30 min. Slowly temperature was raised to 25-35°C and maintained the same temperature for next 30 min; followed by addition of NaCl solution (50g NaCl + 250 ml water) and stirred for 30 min. Layers were separated. Ethyl acetate layer was again washed with solution of Sodium chloride (50 g) and Sodium carbonate (100g) prepared in 250ml water. The Ethyl acetate layer was charcoalised with 2.5g activated carbon followed by filtration through hyflow supercell. The hyflow pad was washed with ethyl acetate (2x25ml). All Ethyl acetate layers are combined and concentrated by removal of Ethyl acetate ca. 45% at 75-80°C. The resulting solution was slowly cooled to 25-40°C, and maintained for 3 hrs. The product was filtered and washed Ethyl acetate (2x12.5 ml) and the cake was dried at 50 – 55°C till constant weight gave 17g of Carvedilol (Recovery =68%).

HPLC Purity = 98.5-99.5%

Impurity Compound (IV) = 0.5-1.0%

MP= 113-116 °

Example: 8

Carvedilol (24 g) (obtained from experiment-7) was heated with ethyl acetate (192 ml) at 60 – 65°C to get a clear solution. To this, activated carbon (2.4 g) was added and stirred at 70 – 75°C for 1 hr. It was filtered hyflow supercell and washed the hyflow supercell with hot ethyl acetate (60–65°C) (2x12 ml). The filtrate and washes were combined and 108 ml ethyl acetate was distilled out at atmospheric pressure. The resulting solution was slowly cooled to 25 – 30°C

and stirred 2 hrs. The product was filtered and washed with ethyl acetate (2x12 ml). The product was dried at 50 – 55°C till constant weight gave 19.5 g. of Carvedilol (Recovery = 81.25%)
HPLC Purity = >99.5%
Impurity compound (IV) = <0.15%
MP = 113-115 °C

Example-9

Preparation of Carvedilol Form –II:

Carvedilol (19 g) (obtained from experiment-8) was heated with ethyl acetate (152 ml) at 60 – 65°C to get a clear solution. To this, activated carbon (1.9 g) was added and stirred at 70 – 75°C for 1 hr. It was filtered hyflo supercell and washed the hyflo supercell with hot ethyl acetate (60–65°C) (2x9.5 ml). The filtrate and washes were combined and 86 ml ethyl acetate was distilled out at atmospheric pressure. The resulting solution was slowly cooled to 25 – 30°C and stirred 2 hrs. The product was filtered and washed with ethyl acetate (2x9.5 ml). The product was dried at 50 – 55°C till constant weight gave 17 g. of Carvedilol (Recovery =89.5%)
HPLC Purity = >99.5%
All individual impurities = <0.10%
MP = 113-116°C
The product obtained from example-9 complies as per EP.

Example:

The process of this invention was carried out with other salts e.g. Benzoate, Oxalate, and, Tartrate of Carvedilol and Carvedilol so obtained was of identical high HPLC purity.

Dated this 19th February 2004

H. SUBRAMANIAM
Of Subramaniam, Nataraj & Associates
Attorneys for the applicants